Endoplasmic reticulum stress in proteinuric kidney disease

Andrey V. Cybulsky[1]

[1]Department of Medicine, McGill University Health Centre, McGill University, Montreal, Quebec, Canada

Endoplasmic reticulum (ER) stress refers to physiological or pathological states that result in accumulation of misfolded proteins in the ER. To handle misfolded proteins, the ER has in place quality control mechanisms, including the unfolded protein response and ER-associated degradation (ERAD). ER stress in renal pathophysiology is a relatively new area of research. Mice heterozygous for a mutation in the ER chaperone, BiP, develop glomerulosclerosis and tubulointerstitial disease. Induction of ER stress in glomerular cells has been described in experimental models of membranous nephropathy and membranoproliferative glomerulonephritis, and exogenous induction of ER stress ('preconditioning') reduced proteinuria. In human kidney biopsies, markers of ER stress in glomeruli have been identified in various noninflammatory and inflammatory glomerulopathies. A tubulointerstitial ER stress response, in some cases associated with tubular cell apoptosis, may occur in glomerular diseases associated with proteinuria, including puromycin aminonucleoside nephrosis, protein overload, and experimental and human diabetic nephropathy. Certain missense mutations in nephrin and podocin, as well as underglycosylation of nephrin, result in misfolding and retention in the ER, and eventually ERAD. Understanding the various aspects of ER stress will provide an opportunity for development of novel therapeutic strategies for proteinuric diseases.

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Correspondence: *Andrey V. Cybulsky, Division of Nephrology, McGill University Health Centre, Royal Victoria Hospital, McGill University, 687 Pine Avenue West, Montreal, Quebec, Canada H3A 1A1.*
E-mail: andrey.cybulsky@mcgill.ca

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The endoplasmic reticulum (ER) is a membranous network that extends throughout the cytoplasm of a cell, and is contiguous with the nuclear envelope. The ER serves as a site for the folding, assembly, and degradation of proteins, as well as for synthesis of steroids, cholesterol, and other lipids. In addition, the ER is a major intracellular storage site for calcium. Secretory, lumenal, and membrane proteins are translocated into the lumen of the ER shortly after initiation of synthesis (Figure 1).[1] These proteins are covalently modified and attain their correctly folded conformation in the ER through ER-resident enzymes and chaperones. Protein folding is catalyzed by peptidyl prolyl isomerases, whereas glycosylation involves glycosidases and mannosidases. Folding-competent states are maintained by classical chaperones, for example, the glucose-regulated proteins (GRP)94 and BiP (GRP78), and lectin-like chaperones, for example, calnexin and calreticulin. ER stress refers to physiological or pathological states, which may increase the demand for protein folding, or disrupt the processes by which proteins fold, resulting in an accumulation of misfolded proteins in the ER lumen. To rescue misfolded proteins, the ER has in place quality control mechanism, including the unfolded protein response (UPR)[1–5] and ER-associated degradation (ERAD).[1,6–8]

UPR

The UPR is a coordinated stress response that upregulates the capacity of the ER to process abnormal proteins (Figure 1).[2–4] The major UPR signaling pathways are initiated by three protein sensors, activating transcription factor-6 (ATF6), inositol requiring-1α (IRE1), and PERK (PKR-like ER kinase). In resting cells, the three sensors are in an inactive state, by association with the ER chaperone, BiP. Upon accumulation of misfolded proteins in the ER, or depletion of ER calcium stores, ATF6 is released from BiP and moves to the Golgi, where it is cleaved by site-1 and site-2 proteases. The cleaved cytosolic fragment, which has a DNA-binding domain (containing the basic leucine zipper motif and a transcriptional activation domain), migrates to the nucleus to activate transcription of ER chaperones and enzymes that promote protein folding, maturation, secretion, and ERAD. In parallel with ATF6, IRE1 autophosphorylates and activates its endoribonuclease activity, cleaving X-box-binding protein-1 (XBP1) mRNA and changing the reading frame

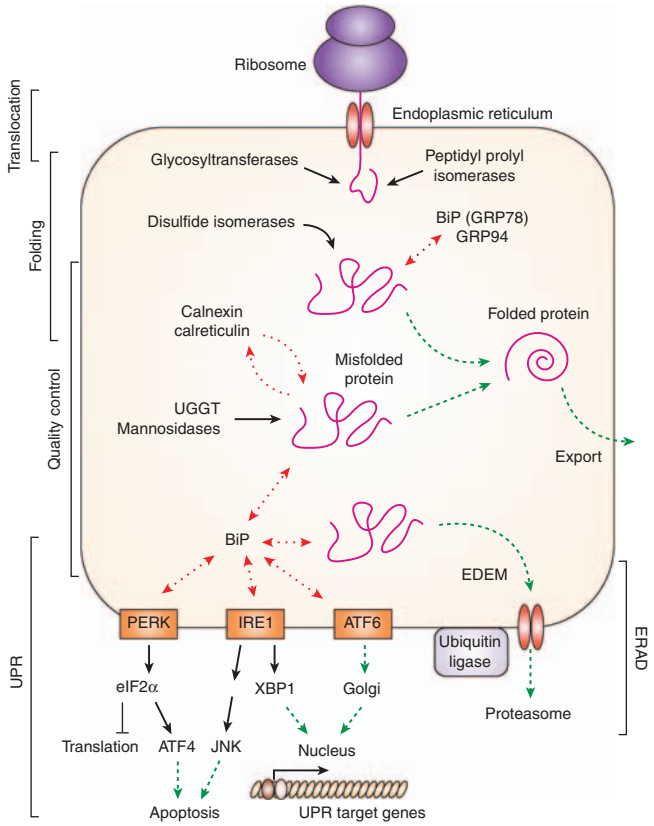

Figure 1 | Protein folding, quality control, and signaling in the endoplasmic reticulum (ER). Solid arrow indicates enzymatic catalysis, dotted arrow indicates an interaction, dashed arrow indicates transport. ATF4, activating transcription factor-4; ATF6, activating transcription factor-6; eIF2α, eukaryotic translation initiation factor-2α subunit; EDEM, endoplasmic reticulum degradation-enhancing α-mannosidase-like protein; ERAD, endoplasmic reticulum-associated degradation; GRP94, glucose-regulated protein 94; IRE1, inositol requiring-1α; JNK, c-Jun N-terminal kinase; PERK, PKR-like ER kinase; UGGT, UDP-glucose:glycoprotein glucosyltransferase; UPR, unfolded protein response; XBP1, X-box-binding protein-1. Adapted from Chevet *et al.*[1]

to yield a potent transcriptional activator. XBP1 functions in parallel with ATF6 to activate transcription of the aforementioned genes. A third aspect of the UPR involves PERK, which is activated through homodimerization and trans-phosphorylation, allowing PERK to phosphorylate the eukaryotic translation initiation factor-2α subunit (eIF2α). This process reduces initiation AUG codon recognition; thus, the general rate of translation is reduced, which aims at decreasing the protein load on a damaged ER. However, selective mRNAs, typically those that contain short open reading frames in the 5′-untranslated region, can be preferentially translated under these conditions. Such mRNAs include ATF4, a transcription factor that can induce expression of UPR target genes. Although BiP may serve as a master regulator of the UPR sensors (ATF6, IRE1, and PERK), more recent studies suggest that IRE1 (and possibly PERK) may bind misfolded proteins directly.[4] Such direct recognition may allow for a more nuanced set of responses.

QUALITY CONTROL AND ERAD

Calnexin and calreticulin are ER chaperones involved in the folding of glycoproteins.[1,7] ER quality control is mediated through recognition of glycan moieties bound to proteins. Unfolded or misfolded proteins are reglucosylated by UDP-glucose:glycoprotein glucosyltransferase (UGGT), and ER mannosidases affect retention time of misfolded proteins with ER chaperones (Figure 1). Calnexin, UGGT, and mannosidases allow misfolded proteins multiple chances to acquire a correctly folded conformation (calnexin chaperone cycle). However, prolonged retention of misfolded proteins leads to ERAD.[6,8] Mannose trimming of N-linked glycan has an important role in ERAD. ER degradation-enhancing α-mannosidase-like protein (EDEM) functions as the mannose$_8$-binding lectin in the ERAD pathway, and is a key molecule that recognizes misfolded glycoproteins. EDEM helps misfolded proteins leave the calnexin cycle toward degradation. The misfolded proteins are retrotranslocated into the cytosol, where they undergo ubiquitination, a covalent modification that marks the protein for destruction by the proteasome. ER stress may upregulate some of the proteins involved in ERAD, for example, EDEM, which lies downstream of IRE1. The UPR and ERAD are intimately linked; thus, UPR induction may increase ERAD capacity, and loss of ERAD may lead to UPR induction.

CONSEQUENCES OF THE UPR

Activation of the UPR appears to be a generalized process occurring in many cell types. In certain cell types, the UPR may be important for normal physiological function, including those cells with a high rate of protein synthesis or whose primary function is the production of secretory- or membrane-resident proteins. Examples include pancreatic-β cells, which require the PERK/eIF2α pathway for maintenance of function and prevention of cell failure, and plasma cells, where the IRE1/XBP1 pathway is necessary for the production of antibodies.[2] As discussed above, induction of the UPR allows cells to recover from stress, and once activated, the UPR may be protective to additional insults.[3,4] In contrast, substantial/prolonged ER stress may be cytotoxic, and lead to apoptosis (Figure 1).[3,4,9] The proapoptotic effector pathways may include the ATF4-mediated induction of C/EBP homologous protein-10 (CHOP/GADD153), a gene transcribed preferentially after eIF2α is phosphorylated by PERK, and the activation of caspase-12, or activation of apoptosis signal-regulating kinase-1 and c-Jun N-terminal kinase, downstream of IRE1 (Figure 1).

ER STRESS IN RENAL PATHOPHYSIOLOGY

The role of ER stress in renal pathophysiology is a relatively new area of research. A few comprehensive reviews on this subject have appeared recently.[10–13] The present review highlights ER stress in conditions primarily involving the glomerulus, focusing on glomerular pathophysiology and potential consequences of proteinuria on renal tubular cells.

NORMAL KIDNEY DEVELOPMENT AND AGING

Several ER chaperones, including BiP and GRP94, are expressed constitutively (in the absence of ER stress), and it is likely that these chaperones are involved in normal protein folding and maturation during development and homeostasis.[14] The understanding of the role of these proteins in normal glomerular development and function is limited. Kimura *et al.*[15] produced a knock-in mouse expressing a mutant BiP, which lacks the ER retention sequence. Homozygous BiP mutant mice suffered from ER stress and died shortly after birth, although the neonatal kidneys appeared normal. In heterozygous mice, there was an increase in tubular atrophy, dilatation, and interstitial fibrosis, as well as glomerulosclerosis at an advanced age (80 weeks). These results suggest that although BiP is not essential for normal kidney development, BiP may be required for maintenance of normal glomerular and tubular architecture.

ER STRESS IN COMPLEMENT C5b-9-MEDIATED GLOMERULAR EPITHELIAL CELL INJURY

Among the first demonstrations of ER stress in glomerular disease are studies on the passive Heymann nephritis (PHN) model of experimental membranous nephropathy.[16,17] In PHN, C5b-9 assembles in glomerular epithelial cell (GEC)/podocyte plasma membranes, 'activates' GECs, and leads to proteinuria and sublytic GEC injury.[18] On the basis of the studies in GEC culture and *in vivo*, C5b-9 assembly induces activation of phospholipases and protein kinases, a decline in cellular adenosine triphosphate, production of reactive oxygen species, and alterations in nephrin expression or function, thereby inducing a permselectivity defect in the glomerular capillary wall. In addition, complement attack may activate pathways that restrict injury or facilitate recovery. Incubation of cultured GECs with sublytic complement induced leakage of BiP and GRP94 from the ER into the cytosol, and this leakage was enhanced by the activation of cytosolic phospholipase A_2-α (cPLA$_2$). This effect of cPLA$_2$ is in keeping with the observation that activation of cPLA$_2$ leads to phospholipid hydrolysis at the membrane of the ER. In parallel, complement increased expression of BiP and GRP94, activation of PERK, phosphorylation of eIF2α, and a reduction in protein synthesis, in a cPLA$_2$-dependent manner. Complement-induced GEC injury was greater in GECs transfected with BiP antisense mRNA, indicating that induction of BiP has a functionally important role in limiting injury. Moreover, fibroblasts from PERK-knockout mice were more susceptible to complement-mediated injury, as compared with wild-type fibroblasts. Thus, induction of ER stress proteins represents a mechanism for protection of cells from sustained complement attack.

Glomerular BiP and GRP94 proteins were upregulated, and phosphorylation of eIF2α was enhanced in proteinuric rats with PHN, compared with normal rats (Figure 2a). Glomeruli of rats that had been injected with a subnephritogenic dose of adriamycin or tunicamycin (i.e., doses that did not induce proteinuria) showed increases in GRP94 and BiP

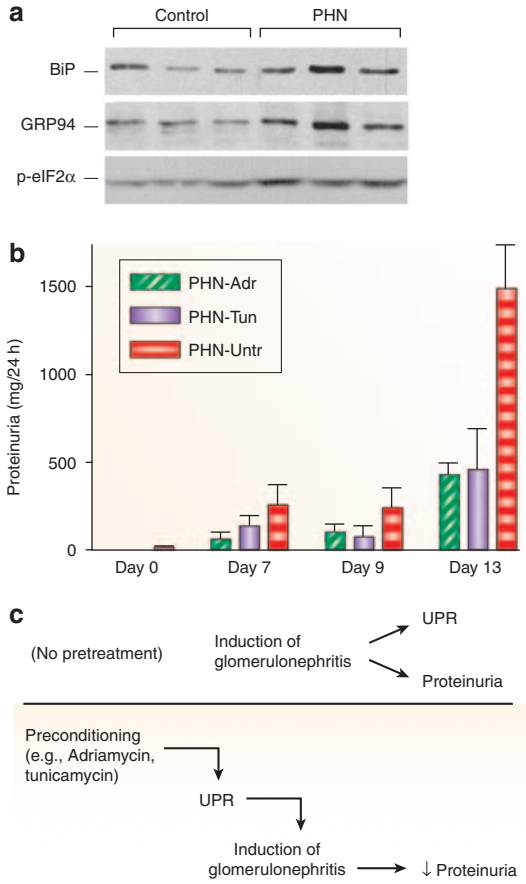

Figure 2 | Endoplasmic reticulum (ER) stress in experimental membranous nephropathy (passive Heymann nephritis; PHN). (**a**) ER stress is increased in C5b-9-mediated podocyte injury. Glomeruli were isolated from normal rats (control) and from rats with PHN on day 14, and lysates were immunoblotted with antibodies to BiP, GRP94, or phospho-eIF2α. (**b**) Preconditioning of rats with a subnephritogenic dose of adriamycin (Adr) or tunicamycin (Tun) reduces proteinuria in PHN. Rats were untreated (Untr), or were injected with adriamycin or tunicamycin to upregulate ER stress proteins. Four days later, rats were injected with nephritogenic antibody to induce PHN (day 0). Urine protein excretion was measured on days 0, 7, 9, and 13. (**c**) Scheme illustrating the effect of ER stress preconditioning on glomerular injury (proteinuria). UPR, unfolded protein response. Panels a and b are from Cybulsky *et al.*,[16,17] with permission.

expression. On the basis of these results, rats were treated with subnephritogenic doses of adriamycin or tunicamycin, and PHN was then induced in both pretreated and untreated rats. Substantial proteinuria developed in untreated rats with PHN, whereas proteinuria was attenuated in the rats that had been pretreated (Figure 2b). Thus, 'preconditioning' to increase ER stress can reduce C5b-9-mediated GEC injury *in vivo* (Figure 2c).

ER STRESS IN OTHER EXPERIMENTAL MODELS OF PODOCYTE INJURY

An increase in the expression of ER stress proteins occured after incubation of cultured GECs with various compounds/conditions, including puromycin aminonucleoside, tunicamycin,

calcium ionophores, *S*-nitroso-*N*-acetylpenicillamine (nitric oxide donor), and *in vitro* ischemia reperfusion.[17,19] *In vivo*, puromycin aminonucleoside nephrosis (PAN) is an experimental rat model of minimal change disease and focal segmental glomerulosclerosis (FSGS), and is characterized by proteinuria and podocyte foot process effacement. In PAN, upregulation of BiP in podocytes was evident at days 4–5, coinciding with the development of proteinuria.[17,20]

A transgenic rat that overexpresses megsin, a member of the serine protease inhibitor (serpin) superfamily, shows accumulation of megsin in the ER of podocytes.[21] In these rats, there was marked upregulation of ER chaperones in podocytes. ER stress in podocytes was associated with cellular injury, as demonstrated by a reduction in synaptopodin and an increase in desmin immunofluorescence staining.[19] In contrast, podocytes of transgenic rats overexpressing a mutant megsin, without the capacity for polymerization within the ER, did not exhibit ER stress or podocyte damage, suggesting a pathogenic role for ER retention of polymerized megsin. Presumably, increases in ER chaperones in PAN and the megsin rat fulfill a cytoprotective role, but this has not been examined directly.

Mutations in the cytoskeletal protein, α-actinin-4, lead to a familial form of FSGS. Mice that develop FSGS due to expression of an α-actinin-4 K256E transgene in podocytes demonstrated glomerular ER stress, including upregulation of ER chaperones, phosphorylation of eIF2α, and induction of the proapoptotic protein, CHOP.[22] Expression of α-actinin-4 K256E in cultured cells enhanced ER stress and apoptosis. ER stress was associated with aggregation and ubiquitination of α-actinin-4 K256E, and 'choking' of the ubiquitin-proteasome system.[3] This may be an example where impairment of the proteasome results in ER stress, possibly by an induced defect in ERAD.

ER STRESS IN PROLIFERATIVE GLOMERULONEPHRITIS

Inagi *et al.*[23] reported on the induction of ER stress in a model of mesangial injury. The authors showed upregulation of the ER chaperones, BiP and ORP150, activation of PERK, and phosphorylation of eIF2α in glomeruli of rats with anti-Thy1 nephritis on day 7 after induction of nephritis, which corresponds to the stage of mesangial hypercellularity. Tunicamycin or thapsigargin given to rats 4 days before induction of anti-Thy1 nephritis did not affect renal pathology or function, although the compounds increased expression of BiP and ORP150. After induction of nephritis (day 3), in the rats preconditioned with tunicamycin or thapsigargin, glomeruli displaying microaneurysms were markedly reduced compared with nonpretreated rats. Moreover, subsequent mesangial proliferation was ameliorated at day 7. Tunicamycin and thapsigargin pretreatment ameliorated increases in glomerular size and glomerular cell number, and was associated with a decrease in proteinuria. It should be noted that there was no improvement in disease manifestations when tunicamycin was injected after induction of anti-Thy 1 nephritis.

The molecular mechanisms by which ER stress is evoked in anti-Thy1 nephritis remain to be elucidated. One proposed explanation is that the mesangial injury initiated by complement activation may induce ER stress in mesangial cells as it does in podocytes. Other mechanisms may also be relevant to this and other forms of proliferative nephritis. Recently, production of cytokines, nitric oxide, and reactive oxygen species has been reported to trigger ER stress.[5,24] There is evidence for crosstalk between ER stress and oxidative stress.[5] Moreover, there appears to be a link between ER stress and nuclear factor (NF)-κB, a key transcription factor, whose activation induces coordinated expression of inflammation-associated genes encoding cytokines, chemokines, adhesion receptors, and so on.[5,24] Various chemical inducers of ER stress can activate NF-κB. Activation may involve ATF6, IRE1, or PERK, as well as the protein kinase, Akt, changes in cytosolic calcium concentration, and generation of reactive oxygen species.[5,24] Alternatively, there is evidence that chronic ER stress may decrease NF-κB activation by inflammatory stimuli.[24,25] Mechanisms may include induction of IκB, C/EBP family transcription factors, the zinc-finger protein, A20, and others. Thus, although ER stress may activate NF-κB in the early phase, more chronic ER stress potentially inhibits NF-κB activation.

EXPRESSION OF ER STRESS MARKERS IN HUMAN KIDNEY BIOPSIES

Several studies have demonstrated increased expression of ER stress proteins in human kidney biopsies. An increase in BiP expression was seen in proteinuric nephropathies, including FSGS and membranous nephropathy[26,27] consistent with findings in experimental animal models. Minimal change disease, FSGS, and membranous nephropathy were associated with increased expression of the proapoptotic protein, CHOP.[26] Biopsies from patients with membranoproliferative glomerulonephritis and rapidly progressive glomerulonephritis showed upregulation of BiP and CHOP.[27] The presence of CHOP suggests that in at least some glomerular diseases, the ER stress response has become proapoptotic, although it should also be noted that CHOP may be upregulated through nonER stress pathways.

TUBULAR EFFECTS OF PROTEINURIA AND THE ROLE OF ER STRESS

Proteinuria in glomerular disease has been postulated to contribute to progressive tubulointerstitial fibrosis, and excessive urinary protein may represent a direct stress to renal tubular epithelial cells. In a cell culture model of proteinuria, it was demonstrated that exposure of tubular epithelial cells to albumin can lead to activation of profibrogenic mechanisms and to tubular cell injury.[28] In proximal tubular cells, albumin induced an increase in BiP and ORP150 expression, as well as apoptosis. Furthermore, these two ER chaperones were upregulated in proximal tubular cells in proteinuric PAN (at 3 weeks), and there was an associated increase in apoptosis.[28] In another study,

protein overload was induced in mice in which BiP was mutated to remove its ER retention sequence[15] (discussed above). After administration of bovine serum albumin to these mice, the heterozygous BiP mutant mice developed severe tubulointerstitial injury, compared with normal mice, despite similar levels of urinary protein excretion. There was associated tubular activation of the proapoptotic, caspase-12, and apoptosis. In experimental type I diabetes induced by streptozotocin (in rats), BiP and CHOP were upregulated in whole kidney homogenates after 4 months of diabetes. This upregulation was associated with an increase in tubular cell apoptosis.[29] Together, these studies support the view that a tubulointerstitial ER stress response occurs due to an increase in filtered proteins, and that the ER stress may be proapoptotic.

To test the hypothesis that proteinuria may induce ER stress in kidney tubular cells in humans, gene expression was analyzed in the tubulointerstitial compartment of renal biopsies of patients with established, proteinuric diabetic nephropathy.[30] For comparison, biopsies with mild diabetic nephropathy and minimal change disease were analyzed, and pretransplantation kidney biopsies served as controls. By microarray analysis, patients with established, but not mild, diabetic nephropathy showed significant increases in tubular mRNA levels of genes involved in the UPR (i.e., BiP, ORP150, XBP1, calnexin, and site-1 protease). In contrast, the mRNA levels of UPR-induced apoptosis mediators, such as CHOP and GADD34, were reduced or undetectable in biopsies from established diabetic nephropathy, compared with the mild form. The results were confirmed in an independent cohort of diabetic biopsies, using quantitative reverse transcriptase-polymerase chain reaction. Moreover, it was shown by immunofluorescence microscopy that BiP and ORP150 proteins were increased in tubular epithelia. Less pronounced increases in some ER stress proteins were observed in tubulointerstitial compartment in minimal change disease. The authors confirmed that the exposure of cultured renal tubular epithelial cells to albumin and high glucose enhanced expression of BiP, ORP150, and XBP1. Thus, the authors proposed that a protective UPR is induced in proteinuric diabetic nephropathy.

ROLE OF THE ER AND ER STRESS IN THE PROCESSING OF SLIT DIAPHRAGM COMPONENTS

Congenital nephrotic syndrome of the Finnish type is an autosomal recessive disorder, which presents with massive proteinuria, already evident *in utero*. The gene responsible, NPHS1, encodes a podocyte-specific membrane protein, nephrin, the principal component of the slit diaphragm.[31] Normally, nephrin is glycosylated and folded in the ER, and transported to the plasma membrane. At least 60 distinct mutations of nephrin have been identified in patients with congenital nephrotic syndrome, the most common being missense mutations resulting in single amino-acid substitutions. Transfection of cells with nephrin cDNAs containing missense mutations showed that a significant number of these proteins accumulated in the ER, and were not transported to the cell surface.[32] Presumably, the mutations result in nephrin misfolding, leading to retention in the ER and ERAD. Sodium 4-phenylbutyrate has been previously shown to function as a chemical chaperone that can correct cellular trafficking of several misfolded mutant plasma membrane proteins, including cystic fibrosis transmembrane conductance regulator and α1-antitrypsin. Treatment of cells expressing some of the nephrin missense mutant proteins with sodium 4-phenylbutyrate resulted in their transport to the plasma membrane, where they functioned indistinguishably from wild-type nephrin.[33] Thus, these nephrin missense mutants escaped ERAD.

Glucose starvation of nephrin-transfected HEK-293 cells resulted in an underglycosylated nephrin that remained in the ER (was not exported to the plasma membrane), and was associated with an increase in BiP expression.[34] The underglycosylated nephrin could be recovered in complexes with calreticulin and calnexin, and to a lesser extent with BiP. Interestingly, treatment of glucose-deprived cells with dexamethasone partially rescued nephrin glycosylation and trafficking, probably through upregulation of genes involved in adenosine triphosphate production and restoration of cellular adenosine triphosphate levels. These results imply that calnexin and calreticulin are involved in nephrin folding in the ER,[7] and the authors suggested that dexamethasone can improve the chaperoning function of calnexin/calreticulin. Treatment of the nephrin-transfected HEK-293 cells with a calcium ionophore also increased BiP expression and underglycosylated forms of nephrin. However, in this context, dexamethasone did not result in recovery of nephrin glycosylation. Further investigation is required to determine whether nephrin underglycosylation is a consequence of ER stress versus glucose deprivation. In another study, it was demonstrated that mizoribine, a purine nucleotide biosynthesis inhibitor with immunosuppressant properties, improved the abnormal processing and localization of nephrin induced by ER stress in cultured cells.[20]

Mutations in the NPHS2 gene encoding podocin are associated with an autosomal recessive type of FSGS and nephrotic syndrome. The R138Q mutation of podocin is a common missense mutation. Although wild-type podocin is localized at the plasma membrane, the R138Q mutant podocin was completely retained intracellularly and colocalized with the ER marker, calnexin.[35] The result suggests that the R138Q mutation affects podocin protein folding. Several other podocin mutations associated with FSGS also resulted in ER retention of podocin.[36] Treatment of cells with the chemical chaperones, glycerol, trimethylamine-*N*-oxide, and dimethylsulfoxide induced redistribution of R138Q podocin to the plasma membrane, although restoration of the function of the protein was not confirmed.[35]

It has also been proposed that nephrin translation is facilitated during ER stress.[17] Phosphorylation of eIF2α by PERK leads to a general reduction in protein translation during ER stress; however, translation of a green fluorescent

protein-reporter regulated by the 5′-end of mouse nephrin mRNA was paradoxically maintained. This effect was most likely due to the presence of short open reading frames in this 5′-flanking mRNA segment, and is in keeping with the observations that translation of mRNAs containing short open reading frames is more efficient after phosphorylation of eIF2α by PERK.[3]

PERSPECTIVES

A number of studies appearing in recent years have demonstrated an association of ER stress with glomerular diseases. A subset of these studies has also demonstrated a functional role for ER stress in disease pathogenesis, and identified previously unrecognized mechanisms. Although the results are intriguing, a better understanding of the various aspects of ER stress will be required for the development of potential therapeutic strategies. There are, however, some obstacles. Experimental models of acquired glomerular disease, particularly models involving podocyte injury or complement activation tend to be more effective in rats, compared with mice, which generally precludes the use of genetic manipulation technology. Moreover, deletion of ER stress genes in mice is frequently lethal, or is associated with abnormal phenotypes.

In experimental models of membranous nephropathy and membranoproliferative glomerulonephritis, ER stress preconditioning reduced proteinuria and renal injury. Although the compounds used for preconditioning may be independently cytotoxic, these results provide a rationale for developing nontoxic methods to induce the activation of UPR pathways *in vivo*, and such efforts are underway.[37] The preconditioning studies imply that upregulation of ER chaperone expression is protective, but it is unknown if such maneuvers would be useful in the treatment of chronic phases of such diseases. A better understanding of the crosstalk and specificity of the UPR pathways is essential. As discussed above, activation of the UPR pathways may be protective, but could also be cytotoxic. These differences may be, in part, related to the specificity of the pathway activated, and/or to the strength of the activating signal. For example, modest-to-moderate activation may be beneficial, although too much activation may be counterproductive.

In glomerular diseases featuring mutations of nephrin or podocin, with consequent protein misfolding, chemical chaperones were on occasion effective in correcting abnormal protein folding and localization. Such studies should encourage the development of specific small molecule pharmacological chaperones. Another area that requires further investigation in these diseases is whether abnormal proteins activate the UPR, including the upregulation of the mediators of ERAD. Instead of activation, suppression of the UPR or ERAD might be beneficial to rescue the function of mutant proteins and retard disease progression. Abnormalities in the folding of slit diaphragm proteins, such as nephrin, may also occur in acquired proteinuric renal diseases. Thus, selective activation of protective aspects of the UPR (e.g., chaperones), but not of other pathways (e.g., ERAD) may be advantageous. Finally, there is increasing recognition that ER stress may be coupled with other cellular processes, such as oxidative stress, inflammation, and autophagy.[5,24,38] These associations introduce more complexity, but they also provide additional opportunities for novel therapeutic approaches.

DISCLOSURE

The author declared no competing interests.

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